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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/919,935	BATHE ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-58* is/are pending in the application.

4a) Of the above claim(s) *9-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants cancellation of claims 1-8 and the addition of new claims 34-58 in the paper of 11/7/2003 is acknowledged. Claims 9-58 are still at issue and are present for examination.

Applicants' arguments filed on 11/7/2003, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 9-33 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 13.

Claim Objections

Claims 34-39, 54 and 56 are objected to because of the following informalities:

Claims 34-39, 54 and 56 are objected to because each of these claims recite a sequence identifier, but the format used in each claim is not consistently used throughout the application (i.e. SEQ ID No: or SEQ ID No.). It is suggested that the format used throughout the application, especially throughout the claims be consistent, such as "SEQ ID No." which also appears elsewhere in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 34 (35-58 dependent from) and 38 are indefinite in that the recitation "b) a polynucleotide which encodes a fragment of a polypeptide which is at least 90% identical to SEQ ID No: 2 and which has methylene tetrahydrofolate reductase activity" is unclear. Specifically it is unclear if the limitation "which is at least 90% identical to SEQ ID No: 2 and which has methylene tetrahydrofolate reductase activity" is a limitation of the encoded fragment or the polypeptide from which the fragment is derived. For the purpose of compact prosecution this portion of the claim is interpreted as the later, that is "b) a polynucleotide which encodes a fragment of a polypeptide, **wherein said polypeptide** is at least 90% identical to SEQ ID No: 2 and which has methylene tetrahydrofolate reductase activity". Applicant is reminded that a single amino acid such as glutamine or alanine is encompassed by a fragment of a polypeptide.

Claims 39, 56 (claims 57 and 58 dependent from) are similarly indefinite as discussed above for claim 34, with respect to what encodes a polypeptide having methylene tetrahydrofolate reductase activity, SEQ ID No. 1 or a fragment of SEQ ID No. 1 or both.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34, 38, 39, 40-44, 46-48, and 50-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection was stated in the previous office action as it applied to previous claims 1-3, 5 and 8. In response to this rejection applicants canceled claims 1-3, 5 and 8 and added new claims 34-58. Newly added claims 34, 39, 40-44, 46-48, and 50-58 are rejected under this statute for the same reasons stated for previous claims 1-3, 5 and 8. For applicants convenience the rejection has been repeated below as it applies to the newly added claims. Applicants have not commented on how this rejection would apply to the newly added claims beyond stating that the rejection would not apply to the newly presented claims which are directed to sequences having at least 90% identity with either SEQ ID NO: 1 or 2.

Claims 34, 39, 40-44, 46-48, and 50-58 are directed to all possible polynucleotides a fragment of a polypeptide which is at least 90% identical to SEQ ID No: 2 and which has methylene tetrahydrofolate reductase activity (See also above 112

2nd paragraph rejection) and polynucleotides which comprise a mere 15 consecutive nucleotides of SEQ ID NO:1.

The specification, however, only provides a single representative species of polynucleotide (i.e. SEQ ID NO: 1) encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these enzymes by any identifying structural characteristics or properties. Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 34,-36, 38, 39, 40-44, 46-48, and 50-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide which encodes a protein having the amino acid sequence of SEQ ID NO: 2, wherein said protein has methylene tetrahydrofolate reductase activity, does not reasonably provide enablement for any polynucleotide which comprises a mere 15 consecutive nucleotides of SEQ ID NO: 1. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection was stated in the previous office action as it applied to previous claims 1-3, 5 and 8. In response to this rejection applicants canceled claims 1-3, 5 and 8 and added new claims 34-58. Newly added claims 34,-36, 38, 39, 40-44, 46-48, and 50-58 are rejected under this statute for the same reasons stated for previous claims 1-3, 5 and 8. For applicants convenience the rejection has been repeated below as it applies to the newly added claims. Applicants have not commented on how this rejection would apply to the newly added claims beyond stating that the rejection would not apply to the newly presented claims which are directed to sequences having at least 90% identity with either SEQ ID NO: 1 or 2.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 34-36, 38, 39, 40-44, 46-48, and 50-58 are so broad as to encompass any polynucleotide which are at least 90% identical to a polynucleotide which encodes the amino acid sequence of SEQ ID NO: 2 or any polynucleotides which comprises a

mere 15 contiguous nucleotides of SEQ ID NO: 1 and host cells and vectors comprising said polynucleotides.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. The claims rejected under this section of U.S.C. 112, first paragraph, place insufficient structural and functional limits on the claimed polynucleotides. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The same is true of a polynucleotide sequence, as the nucleic acid sequence of the polynucleotide directly correlates with the amino acid sequence of the polypeptide. However, in this case the disclosure is limited to a polynucleotide which encodes a protein having the amino acid sequence of SEQ ID NO: 2.

While recombinant and autogenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a polynucleotides sequence where nucleic acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any polynucleotide and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any

tolerance to modification for a given polynucleotide to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass those polynucleotides having the claimed structural relationship to SEQ ID NO: 1, because the specification does not establish: (A) regions of the polynucleotide structure which may be modified without effecting the desired activity; (B) the general tolerance of the claimed polynucleotides to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleic acid residue of SEQ ID NO: 1 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the desired activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birdhouse, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those polynucleotides of the claimed genus.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any polynucleotide with the claimed

structural relationship to SEQ ID NO: 1. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34, 38, 39, 41-44, 46, 51, 53, 55 and 56-58 are rejected under 35 U.S.C. 102(b) as being anticipated by Blanco et al. (Journal of Bacteriology, Vol. 180, No. 6, pp 1586-1591, March 1998, See IDS).

Blanco et al. teach the *Streptomycin lividness* methylene tetrahydrofolate reductase gene which comprises a polynucleotide sequence that encodes a fragment (i.e. glutamine or alanine, as discussed above under 112 2nd paragraph rejection) of a polypeptide, **wherein said polypeptide** is at least 90% identical to SEQ ID No: 2 and which has methylene tetrahydrofolate reductase activity. Blanco et al. further teach vectors and host cells comprising said polynucleotide and methods of its expression.

While it is admitted that the polynucleotide sequence taught by Blanco et al. is not itself 90% identical to a polynucleotide which encodes SEQ ID NO: 2, it does encode a fragment (i.e. glutamine or alanine) of SEQ ID NO: 2 and the encoded polypeptide has methylene tetrahydrofolate reductase activity. Thus claims 34, 38, 39, 41-44, 46, 51, 53, 55 and 56-58 are anticipated by Blanco et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Blanco et al. (Journal of Bacteriology, Vol. 180, No. 6, pp 1586-1591, March 1998, See IDS).

As discussed above, Blanco et al. teach the *Streptomycin lividness* methylene tetrahydrofolate reductase gene which comprises a polynucleotide sequence that encodes a fragment (i.e. glutamine or alanine, as discussed above under 112 2nd paragraph rejection) of a polypeptide, **wherein said polypeptide** is at least 90% identical to SEQ ID No: 2 and which has methylene tetrahydrofolate reductase activity. Blanco et al. further teach vectors and host cells comprising said polynucleotide and methods of its expression.

One of ordinary skill in the art at the time of filing would have been motivated to express the polynucleotides taught by Blanco et al. as an RNA, so that the encoded proteins could be produced, in order to study the mechanism of actions of each of the

identified enzymes involved in motioning biosynthesis in *Streptomycin lividness*. As a necessary step in the production of the encoded protein, a mina copy of the taught polynucleotides is first generated. The reasonable expectation of success comes from the high degree of knowledge in the art of heterologous *in vitro* protein expression as supported by the number of commercially available in vitro transcription/translation kits.

Conclusion

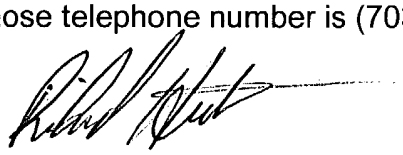
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
2/3/2004